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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Jane Massey Licata, Esquire
Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053

EXAMINER	
KLINKEL, KORTNEY L	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,657	RUNGE ET AL.	
	Examiner	Art Unit	
	Kortney L. Klinkel	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-41,46 and 49-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-41, 46, and 49-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/17/2009 has been entered.

Claims 37-41, 46, and 49-62 are pending. Claims 1-36, 42-45, 47-48 stand canceled.

Withdrawn Claim Objections/Rejections

Claim Objections

The objection to claims 39 and 61-62 because of the following informalities: The word **mixer** is misspelled **mixture** in these claims is withdrawn in light of the claim amendments.

Claim Rejections - 35 USC § 112 2nd Paragraph

The rejection of claim 42 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of the cancellation of claim 42.

Claim Rejections - 35 USC § 112 1st Paragraph

The rejection of claim 50 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the free acid amid form of flutamide, does not reasonably provide enablement for pharmaceutically acceptable solvates of flutamide is withdrawn in light of the claim amendments to remove recitation of solvates of flutamide.

Claim Rejections - 35 USC § 102

The rejection of claims 37-40, 42-43, 47-48, 50-62 under 35 U.S.C. 102(b) as being anticipated by James et al. (US 6228401, as per Applicant's IDS) is withdrawn in light of the claim amendments which impart the limitations of claim 44 (now canceled) into independent claim 37.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 46 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 46 currently depends from canceled claim 45 and claim 49 currently depends from canceled claim 48. As a results, the metes and bounds of claims 46 and 49 are unclear. In an effort to expedite prosecution, claims 46 and 49 are being treated as if they depended from independent claim 37.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 37-40, 46, and 49-6237-40, 42-43, 47-48, 50-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over James et al. (US 6228401, as per Applicant's IDS).

The instant claims are drawn to a pharmaceutical formulation comprising crystalline and/or amorphous flutamide particles mixed with at least one surface-active substance wherein the size of 50% of the flutamide particles in the pharmaceutical formulation is greater than 26 μm (claim 37).

James et al. teach a pharmaceutical formulation comprising crystalline and/or amorphous flutamide particles mixed with at least one surface-active substance (Examples 6, 7, and 9). James does not explicitly state that the flutamide is crystalline and/or amorphous, however, because there are no other known forms that flutamide can be in, it must be crystalline and/or amorphous. The surface active substance is sodium lauryl sulfate which is an anionic compound as per claim 51. Sodium lauryl sulfate is the common name for sodium dodecylsulfate, as required by claim 52. James teaches that rotary cutters are one means of achieving the desired flutamide particle size (col. 2, lines 37-38). Rotary cutters are a type of forced-action mixer; the blades are forced through the desired mixture. The instant specification at page 10, 3rd paragraph provides support for this statement. This paragraph states that "Conventional forced-action mixers with a stainless steel interior may be used for the process according to the invention. Forced-action mixers are generally mixers having a round or flat base and blades or paddles rotating close to the base. They may have so-called "choppers", that is, rapidly rotating knives, which project into the mixing vessel."

With respect to claims 38, 40 and 56, James teaches the formulation in the form of a tablet with at least one flow regulator (silica) in example 7. The tablet of example 7 could also be used as a suppository. The term suppository is an intended use and

because the prior art structure is capable of performing the intended use, it meets the limitations of the claim, absent evidence to the contrary. With particular respect to claim 56, a tablet is considered a shaped article.

With respect to claim 39, James teaches the formulation as filling for capsules in examples 6 and 9.

With respect to claim 50, James teaches the flutamide is in the form of its free acid amide or a pharmaceutically acceptable salt thereof (col. 2, lines 4-5).

With respect to claims 53-55 which specify the weight ratio of flutamide to surface-active substance, James teaches a ratio of flutamide to surface-active substance of 10.4 to 1 which falls within, and thereby anticipates the ranges for claims 53-55 (Example 6).

With respect to claims 57-59 which specify the amount of flutamide in the formulation, James teaches 125 mg of flutamide in the formulation which falls within and thereby anticipates the amounts claimed (Example 6).

With respect to claim 60, all of the working examples of James comprise at least one excipient selected from inorganic fillers, organic fillers, binders, glidants, lubricants, flow regulators and disintegrants. See particularly Example 6 which further comprises lactose, povidone, corn starch, magnesium stearate and water in addition to flutamide and the surface-active substance sodium lauryl sulfate.

As discussed above, James et al. teach the exact same ingredients as required by the instant claims as well as the use of rotary cutters which is a type of forced-action mixer, which is the same process recited in the instant product-by-process claims.

James et al. fails to explicitly teach wherein the size of 50% of the flutamide particles in the pharmaceutical formulation is greater than 26 microns as required in independent claim 37, or wherein 90% of the flutamide particles is greater than 130 microns as required by claim 46, or that the specific surface area less than 0.35 m^2/cm^3 as required by claim 49.

However, James et al. with respect to particle size and surface area teaches the following. James teaches specific examples wherein the X_{50} value of the flutamide particles is greater than 20 μm (example 5, column 7, see example 3 from the table at lines 45-47, X_{50} = 20.99 μm), and an example wherein the flutamide particles have a specific surface area of 0.47 m^2/cm^3 (example 5, column 7, see example 3 from the table at lines 45-47). James more generally teaches that the X_{50} for the particles is less than 26.0 μ (col. 2, lines 23-24) and that typical X_{90} values for the particles is from about 10 to about 130.0μ (col. 2, lines 28-29). With respect to claim 49 which specifies that the flutamide particles have specific surface area of 0.35 m^2/cm^3, James teaches flutamide particles having a specific surface area of at least about 0.35 m^2/cm^3. About 0.35 m^2/cm^3 overlaps with and thereby makes obvious the claimed value of less than 0.35 m^2/cm^3. James et al. teach that means of achieving these particle sizes, distributions and surface areas include milling, but also the use of rotary cutters (i.e. forced-action mixer, see discussion above regarding page 10 of the instant specification), see col. 2, lines 37-38. Also, James teaches that particles of flutamide are known that range from 5 to 240 microns in size (col. 1, line 47). It is also well known in the art that that varying the mixing speed, the amount of flutamide fed into the mixer

and the mixing period all influence the resulting size and surface area of the resultant flutamide particles. James also teaches that flutamide is relatively insoluble (col. 1, line 38) and that flutamide has a consistency which is difficult to mill due to the fact that it readily agglomerates and give inconsistent results (col. 2, lines 46-48). James teaches that the specific surface area of flutamide is critical for determining bioavailability of flutamide (col. 1, lines 52-54). James also teaches that the range of particle sizes contained in a sample of flutamide influences the bioavailability and thus the therapeutic benefit of the drug (col. 2, lines 17-20).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to arrive at particles with an X_{50} value greater than 26 microns and X_{90} values greater than 60 microns or 130 microns and particles with a specific surface area of less than $0.35 m^2/cm^3$ based on the teachings of James at the time of the instant invention with a reasonable expectation of success. One would have been motivated to do so because James teaches X_{50} and X_{90} values and specific surface areas that overlap with, or are very close to those ranges claimed by applicant. Furthermore, James teaches that flutamide is known to exist in particle sizes up to 240 microns and also teaches that it is known in the art to achieve similar particle sizes, as measured by X_{50} and X_{90} values, and different specific surface areas by using rotary cutters or other milling techniques. The rotary cutters technique is a means of intensive mixing in a forced-action mixer as evidenced by the instant specification at page 10 (as discussed in more detail above). Therefore, James et al. teach the exact same ingredients and mixing technique as required by the instant product-by-process claims.

One of ordinary skill in the art would need merely to adjust the speed of the mill or cutter and the amount of flutamide fed into the machine and/or the grinding period (col. 2, lines 39-42) in order to arrive at the instantly claimed particle sizes and surface areas. Furthermore, because it is well known in the pharmaceutical art that milling/mixing is highly energy intensive and therefore costly, and that bioavailability is known to be critically dependent upon both the particle size distribution and the surface area of the resultant particles, one would be particularly motivated to experiment with these features in order to arrive at a set of flutamide particles with optimal bioavailability achieved with optimal efficiency. Further motivation for milling/mixing less and thus arriving at larger particle sizes (i.e. X_{50} greater than 26 microns, X_{90} greater than 130 microns, and a surface area greater than 0.35 m^2/cm^3 stems from the fact that it is well known in the flutamide formulating art that excess milling/mixing can lead to heat degradation of the product. See col. 2, lines 33-34. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

It is important to note that the phrases "unmilled" with respect to flutamide and "wherein the flutamide has been subjected to intensive mixing in a forced-action mixture [mixer] with the at least one surface-active substance" of claim 37 and "wherein the formulation is mixed in a forced-action mixer for 1 to 180 minutes" in claim 61, and "wherein the formulation is mixed in a forced-action mixture [mixer] for 3 to 60 minutes" of claim 62 are recitations of product-by-process limitations. Since claim 37 is a

product-by-process claim, and all pending claims depend from claim 37, therefore, all pending claims are product-by-process claims. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). For more information regarding product-by-process claims, please refer to MPEP 2113. Because James et al. teaches compositions having the exact same ingredients as required by the instant claims, the exact same means of mixing as recited in the instant product-by-process type claims, and further teaches that it is well known in the flutamide formulation art that varying the mixing speed, the amount of flutamide fed into the mixer and the mixing period all influence the resulting size and surface area of the resultant flutamide particles, the limitations of these product-by-process claims is met. It would be obvious to one of ordinary skill in the art to adjust the mixing time. One would be motivated to do so in order to affect the resultant particle size. As discussed above, this particle size has been made obvious over the teachings of James et al.

Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over James et al. (US 6228401) in further view of Neri et al. (US 3995060), both as per Applicant's IDS.

The teachings of James et al. are set forth above. James fails to explicitly teach that the flutamide has been subjected to recrystallization as necessitated by claim 41. Neri '060 teaches pharmaceutical formulations comprising flutamide (4-nitro-3-trifluoromethylisobutyranilide), which is necessarily either crystalline and/or amorphous, sodium lauryl sulfate (a surface-active substance) which are mixed in a bowl (column 17, lines 14-16). The mixture is not milled until subsequent steps (see column 17, lines 17-20). Furthermore, step 3 (lines 21-23) admits that the first milling contains unmilled fractions of flutamide and sodium lauryl sulfate. Neri teaches that recrystallization is a common and effective means of purifying flutamide (col. 2, line 37).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention based on the combined teachings of James and Neri to arrive at the instant formulation comprising recrystallized flutamide with a reasonable expectation for success. One would have been motivated to do so because Neri teaches that recrystilization is a common means of purifying flutamide. Since the desired composition is for pharmaceutical use, one would be particularly motivated to have a pure substance. The more pure the drug, in this case flutamide, the fewer chances for undesired side-effects.

Applicant's data in the specification has been considered. The pharmaceutical formulations shown in working examples 1 through 6 all consist of ingredients identical to those shown in the working examples of James et al., namely flutamide, lactose, sodium lauryl sulfate (a.k.a. sodium dodecylsulfate), microcrystalline cellulose, corn

(maize) starch, silica and magnesium stearate. Example 1 contains crystalline, unmilled flutamide and was intensively mixed for 3 minutes in a forced-action mixer. As discussed in the above rejection, James teaches that forced-action mixers (i.e. rotary cutters) are a means of mixing the flutamide mixture. Subsequent examples use either crystalline unmilled flutamide, micronized flutamide. Different mixing mechanisms are used, including a forced-action mixer, a free fall mixer etc. As taught in James, several different known milling and mixing all techniques give rise to different particle sizes, size distribution and surface areas, and these particle qualities can be easily manipulated by adjusting the speed of the mill, the amount of flutamide fed into the mill and the grinding period. Applicant's specification provides no examples or data demonstrating that the size of the flutamide of the instantly claimed formulations is somehow unexpectedly different or beneficial over that which would be expected from the teachings of the prior art.

Response to Arguments

Applicant's arguments filed 6/17/2009 regarding the rejection of claims have been fully considered, but are moot in light of the new grounds of rejection. However, the examiner will address those issues relevant to the rejection of claims in view of James et al. (US 6228401) alone and also in further view of Neri et al. (US 3995060).

Applicant argues that James et al. teaches away from the present invention and therefor cannot render the claimed invention obvious. More specifically applicant argues that because James teaches milling to achieve the specific surface areas and X_{50} and X_{90} values set forth therein that the skilled person would consider milling

essential to achieve bioavailability of the relatively insoluble flutamide API and they therefore wouldn't be motivated to adjust the size and surface area. In support of this argument applicant points to col. 1, line 64-col. 2 line 3 wherein James et al. discuss that significant research was conducted in order to determine optimal size and surface area of flutamide based on blood levels of the drug. These arguments are not persuasive. As addressed in the above rejection, James teaches X_{50} and X_{90} values that overlap with those values claimed and specific surface areas that are very close to those ranges claimed by applicant. Furthermore, James teaches that flutamide is known to exist in particle sizes up to 240 microns and also teaches that it is known in the art to achieve similar particle sizes, as measured by X_{50} and X_{90} values, and different specific surface areas by using rotary cutters or other milling techniques. Furthermore, because it is well known in the pharmaceutical art that milling/mixing is highly energy intensive and therefore costly, and that bioavailability is known to be critically dependent upon both the particle size distribution and the surface area of the resultant particles, one would be particularly motivated to experiment with these features in order to arrive at a set of flutamide particles with optimal bioavailability achieved with optimal efficiency. Further motivation for milling/mixing less and thus arriving at larger particle sizes (i.e. X_{50} greater than 26 microns, X_{90} greater than 130 microns, and a surface area greater than 0.35 m^2/cm^3) stems from the fact that it is well known in the flutamide formulating art that excess milling/mixing can lead to heat degradation of the product. It is noted that applicant has not provided data demonstrating the unexpected properties of a larger particle size.

In summary, James et al. teaches compositions having the exact same ingredients as required by the instant claims, the exact same means of mixing as recited in the instant product-by-process type claims, that bioavailability depends on the surface area and size distribution of the flutamide particles, and further teaches that it is well known in the flutamide formulation art that varying the mixing speed, the amount of flutamide fed into the mixer and the mixing period all influence the resulting size and surface area of the resultant flutamide particles. Accordingly, as discussed in greater detail above, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to arrive at the claimed invention with a reasonable expectation for success. Applicant has not provided evidence proving that the claimed particle sizes and surface areas are somehow unexpected over the teachings of James et al.

Conclusion

Claims 37-41, 46, and 49-62 are rejected. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kortney Klinkel whose telephone number is (571)270-5239. The examiner can normally be reached on Monday-Friday 8am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached at (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KLK

/Sharmila Gollamudi Landau/
Supervisory Patent Examiner, Art Unit 1611